Synopsis

CHAPTER I: This chapter describes the introduction, earlier synthetic approach and present synthesis of Brefeldin a.

Section A:

Introduction: Brefeldin a (Figure **1)** was isolated in 1958 from *Penicillium decumbens* and later from other fungal strains such as *Penicillium brefeldianum* and *Phyllosticta mediaginis*. Its structure was established in 1971. Brefeldin a has been shown to possess a range of biological activities including antiviral, antibiotic, antifungal and antimitotic activities.

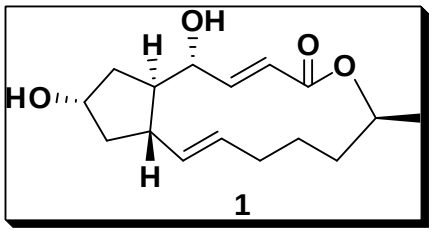


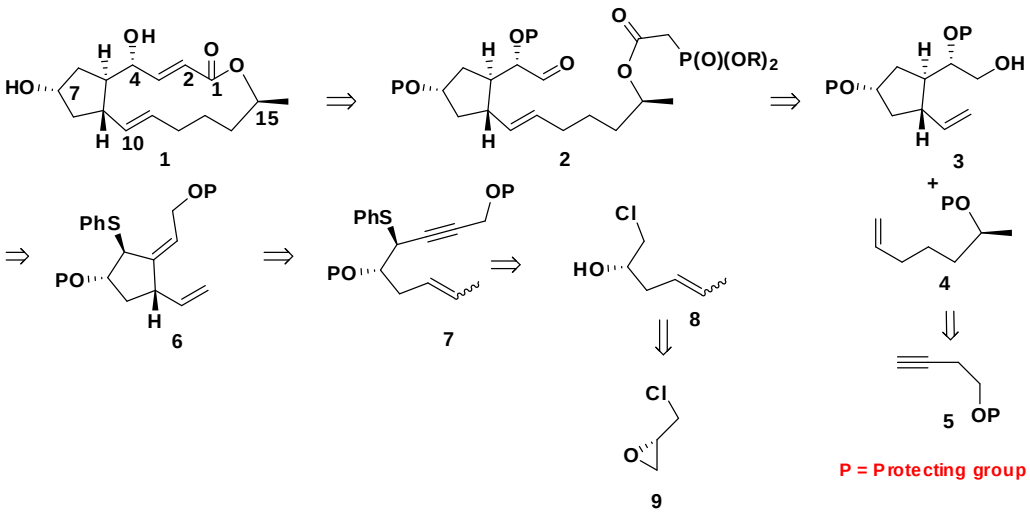
Figure 1: Structure of Brefeldin a

Section B:

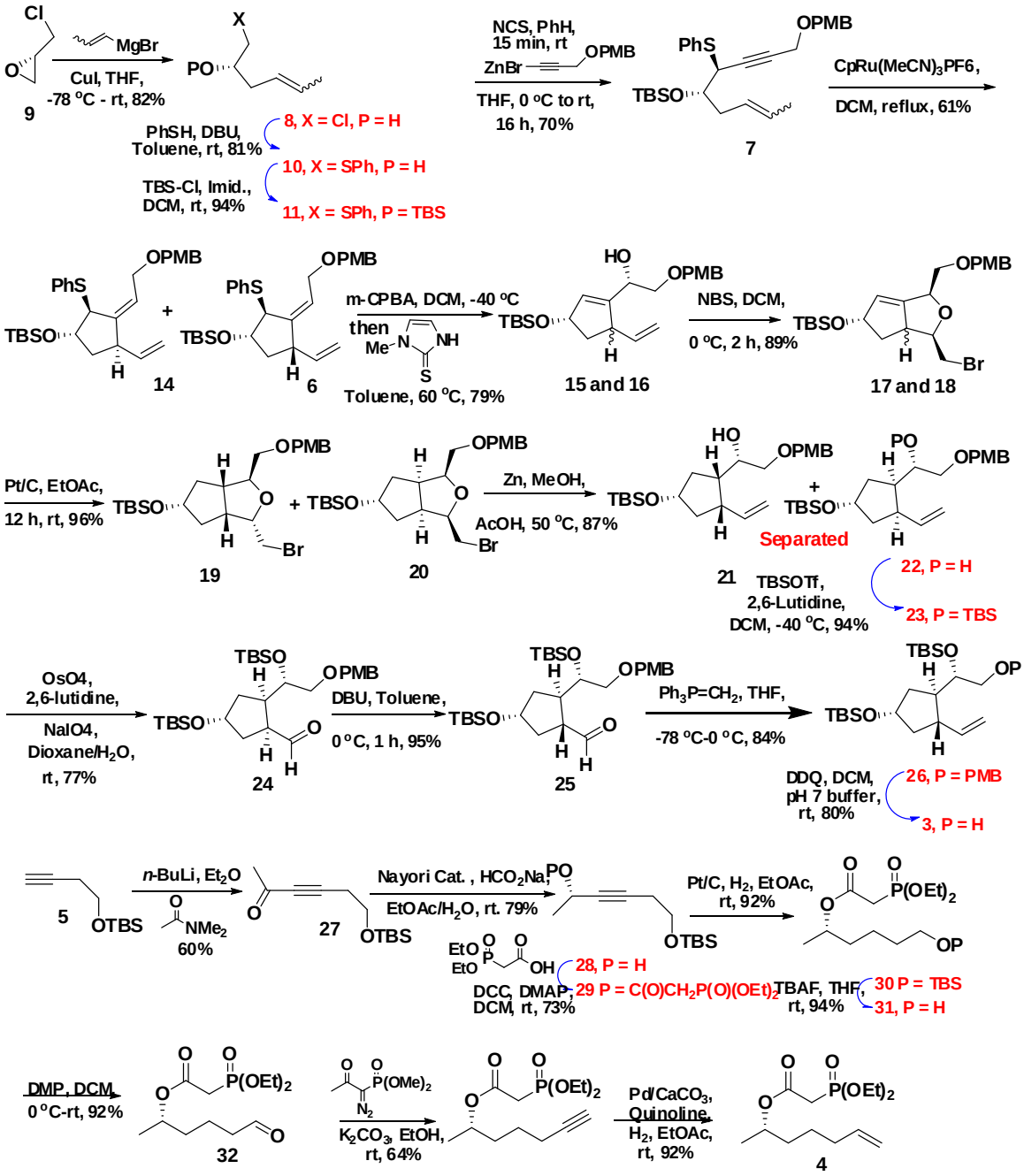
Statement of Problem: The combination of wide biological activity and unique structural features has made brefeldin a an attractive synthetic target. Impressive strategies and routes designed for the assessment of new synthetic methods have been reported by several groups. Many of the approaches include macrolactonization for the formation of the 13-membered ring. Herein, we report the total synthesis of brefeldin a utilizing the HWE-olefination to form the macrocycle, cross-metathesis to create the C10-C11 alkene and Ru(II)-catalyzed enyne cyclization to construct the five-membered ring.

Results and Discussion:

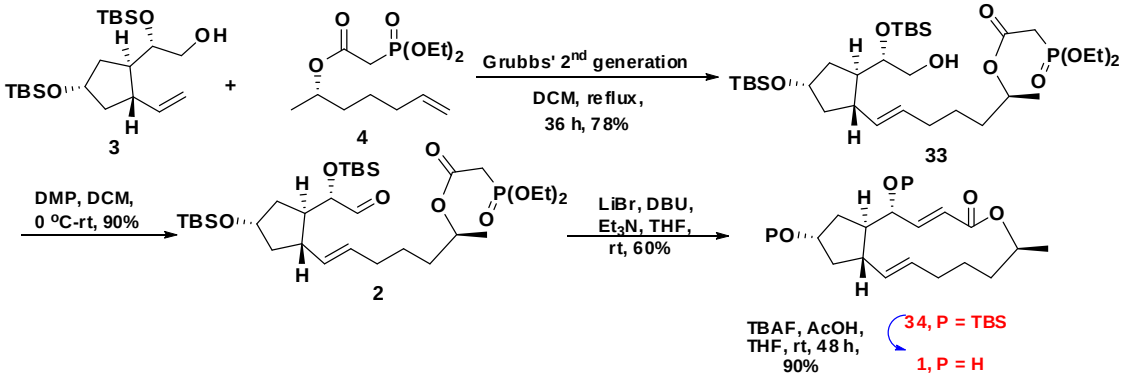
Methodology used (Retrosynthetic analysis):



Scheme 1: Retrosynthetic analysis of Brefeldin a



Scheme 2: Synthesis of Cross-metathesis partners 3 and 4



Scheme 3: Synthesis of Brefeldin a

Conclusion: In summary, a stereoselective synthesis of brefeldin a is disclosed. The key steps of the synthesis include the stereoselective preparation of a propargylic sulfide using an α-chloro sulfide intermediate, stereoselective enyne cycloisomerization using a Ru(II) catalyst, Mislow-Evans rearrangement to create the C-4 carbinol center, selective reduction of an internal alkene by bromoether formation, cross-metathesis for the creation of C10-C11 double bond and macrolactonization by HWE olefination.

<u>CHAPTER II</u>: This chapter describes the introduction, earlier synthetic approach and studies towards the synthesis of Fumagillol.

Section A:

Introduction: Fumagillin, isolated in 1949 by Elbe and Hanson from the microbial organism Aspergillus fumigatus, was originally described as an antimicrobial agent, but in 1990, it was reported to be a potent, selective inhibitor of angiogenesis. More recently, fumagillin has been found to reverse the growth inhibitory activity of viral protein R (Vpr) in yeast and human cells, and to inhibit the HIV-1 infection of human macrophages.

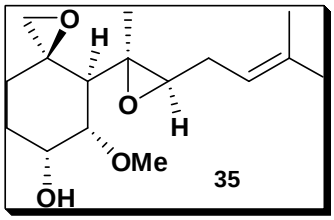
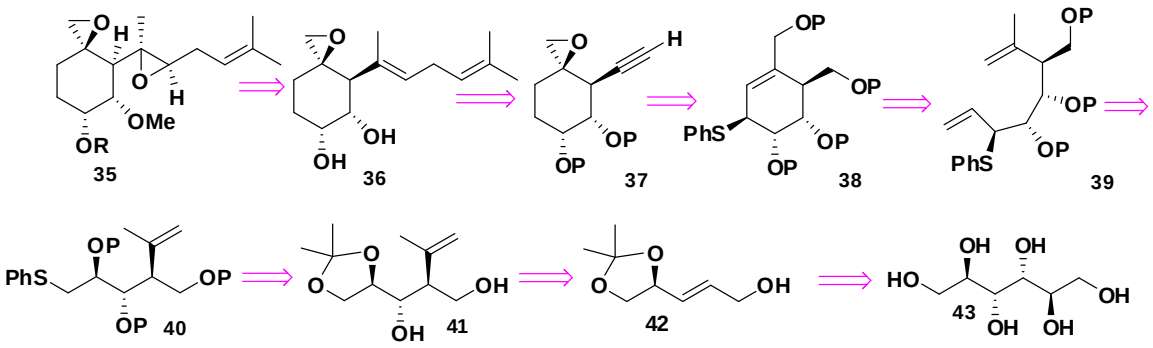


Figure 2: Strucure of Fumagillol

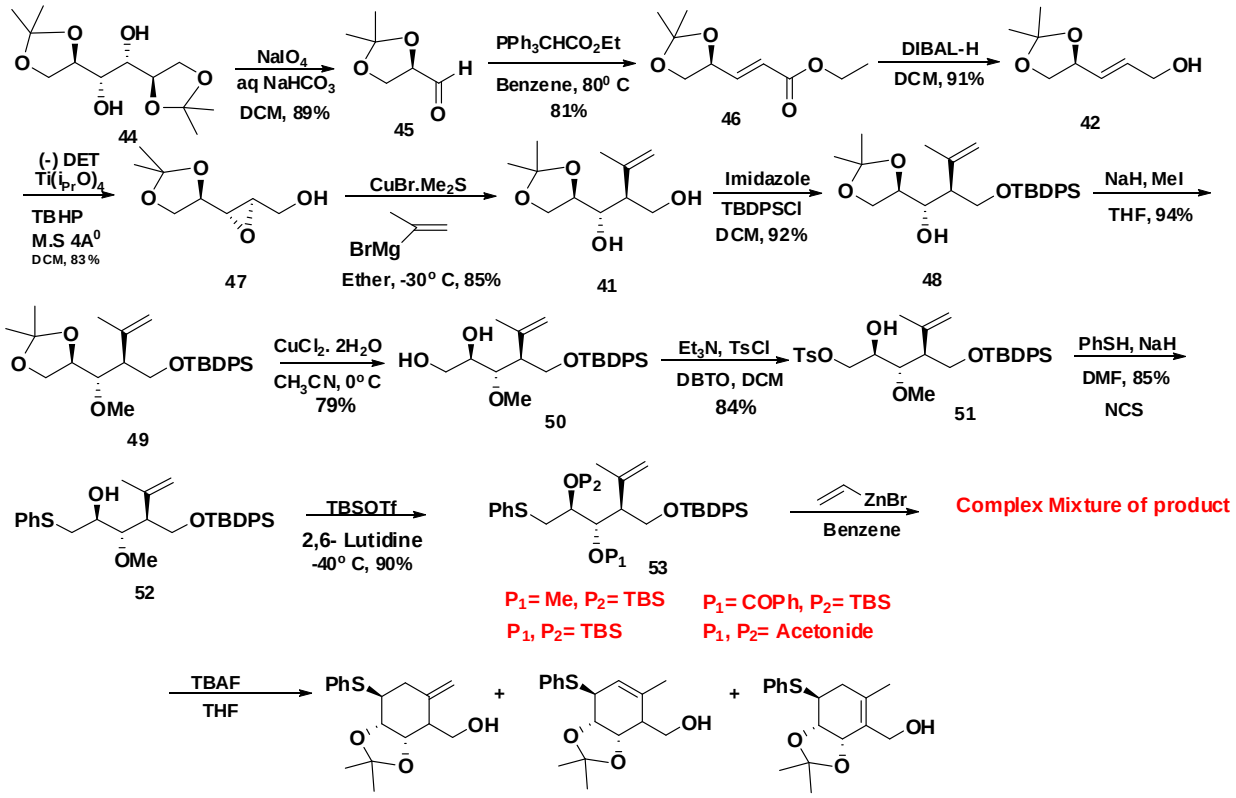
Section B:

Statement of Problem: Fumagillol is comprised of a cyclohexane framework, two epoxides, and six contiguous stereogenic centers, four of which are situated on the cyclohexane ring. As a result of their unique structure and important biological properties, the fumagillin has been pursued as attractive synthetic target. Herein, we utilized the Sharpless epoxidation followed by opening to generate OMe stereogenic center, Ene reaction to form the cyclohexane skeleton and Ohira Bestmann reaction for extentended sidechain.

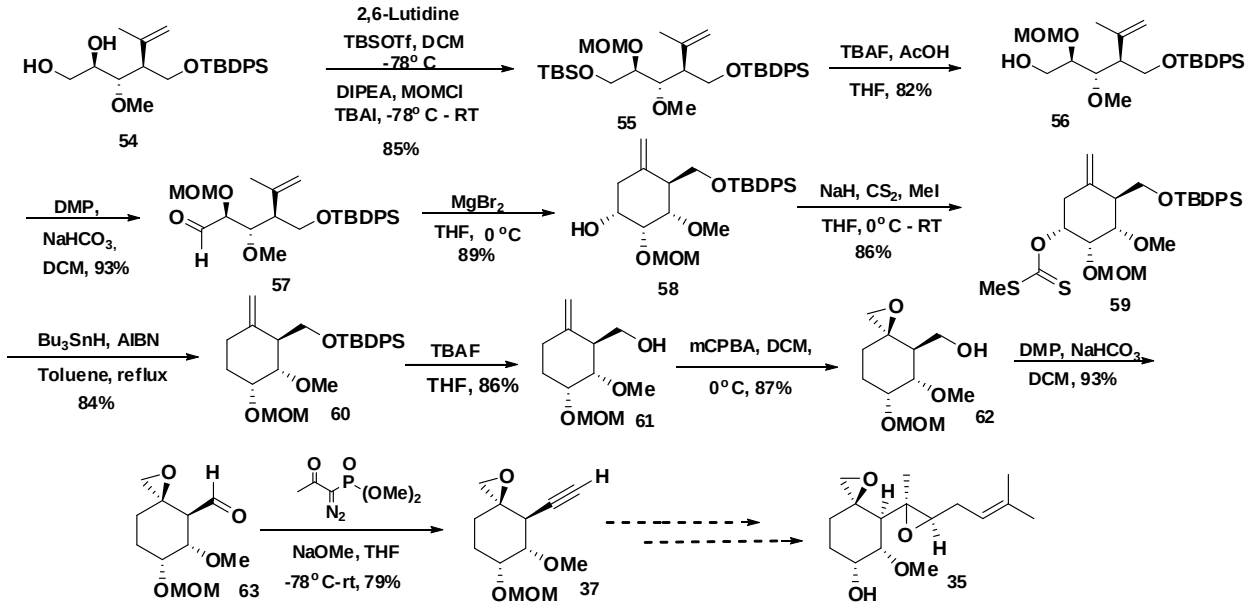
Results and Discussion: Retrosynthetic analysis:



Scheme 4: Retrosynthetic analysis of Fumagillol



Scheme 5: Failed route for the synthesis of Core fragment.



Scheme 6: Forward steps for the synthesis of Core fragment.

Conclusion: We have successfully synthesized cyclohexane skeleton of Fumagillol contain four contiguous streocenters. The key steps involved are Sharpless epoxidation followed by openining with isopropenylmagnesiumbromide using CuBr.Me_2S, Ene reaction for cyclohexane skeleton, stereo selective epoxidation using mCPBA and Ohira Bestmann reaction.